EVALUATION OF HAEMATOLOGICAL ABNORMALITIES IN DECOMPENSATED CHRONIC LIVER DISEASE PATIENTS

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COIMBATORE

CERTIFICATE

This is to certify that the Dissertation entitled ***" Evaluation Of Haematological Abnormalities In Decompensated Chronic Liver Disease Patients",*** *herewith submittedby* ***Major. Dr.T.Vijay,*** *Post Graduate in General Medicine, Coimbatore Medical College to the Tamilnadu Dr. M.G.R. Medical University is a record of a bonafide research work carried out by him under my guidance and supervision from Jan 2006 to Jun 2007.*

Professor Dr. S. Prabha
Prof. and Unit Chief

Prof. Dr. K. Umakanthan
Prof. and Head
Department of Medicine

DEAN

DECLARATION

I solemnly declare that the Dissertation titled ***"Evaluation Of Haematological Abnormalities In Decompensated Chronic Liver Disease Patients ",*** *was done by me at Coimbatore Medical College & Hospital during the period from Jan 2006 to Jun 2007 under the guidance and supervision of Prof. Dr. K. Umakanthan and Prof. Dr. S.Prabha.*

This dissertation is submitted to the Tamilnadu Dr. M.G.R. Medical University towards the partial fulfillment of the requirement for the award of M.D. Degree (Branch I) in General Medicine.

Place : Coimbatore **Dr. T. Vijay**
Date :

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CONTENTS

INTRODUCTION

The essential functions of many organs in the body depend directly or indirectly on the liver. The haemopoietic system is not an exception. Beginning early in the foetal life, it exerts a profound influence on the formation and maintenance of blood. Before birth it acts as a haemopoietic organ and after birth it plays an active and important role in the production of many elements necessary for homeostasis and haematopoiesis. When the liver is damaged by either acute or chronic disease, the effect on these functions may be catastrophic.

Liver plays a major role in carbohydrate metabolism, lipid metabolism and protein metabolism. Its role in hematological manifestations is important. Loss of Liver function can manifest as subtle metabolic abnormalities and derangements in hematological parameters which can ultimately culminate in grave complications[1].

Liver plays a major role in maintaining the hematological parameters and maintain the homeostasis. Liver is the storage site for iron vitamin B_{12} and folic acid which are necessary for the normal

hematopoiesis[2]. Liver also secretes the clotting factors and the inhibitors and keep the homeostasis in equilibrium.

Chronic Liver disease is usually accompanied by hypersplenism[2]. Diminished erythrocyte survival is frequent. In addition both parenchymal hepatic disease and cholestatic jaundice may produce blood coagulation defects. Dietary deficiencies, alcoholism, bleeding and difficulties in hepatic synthesis of proteins used in blood formation or coagulation add to complexity of the problem.

Spontaneous bleeding, bruising and purpura together with a history of bleeding after minimal trauma such as venepuncture, are most important indications of bleeding tendency in patients with liver disease than lab tests[2].

The hematological abnormalities in a chronic disease add morbidity to the primary pathology and increase the mortality. Hence it becomes necessary to investigate the hematological abnormalities and haemostatic abnormalities to decrease the co morbidity.

The study was conducted to assess the hematological abnormalities and haemostatic derangements and the nature of hematological abnormalities to reduce the morbidity. Broadly the hematological abnormalities are viewed under:

1. Abnormalities of formed element.

a. RBCs

b. WBCs

c. Platelets

2. Coagulation abnormalities:

a. Impaired synthesis of clotting factors.

b. Decreased inactivation of activated factors.

AIM OF THE STUDY

1. To study the hematological abnormalities in decompensated chronic liver disease patients.
2. To find out the incidence and type of anaemia in chronic decompensated liver disease patients.
3. To detect the abnormalities in RBCs WBC in cirrhotic patients.
4. To detect platelet abnormalities.
5. To assess the function of clotting factors in the patients with cirrhosis.
6. To correlate the hematological findings with the severity of the disease.

REVIEW OF LITERATURE

LIVER

Liver is one of the largest organs in the body. It is the largest organ weighing about 1200 – 1500 gm, about one fifth of total adult body weight. Liver is divided into 8 functional segments by various planes[2]. They are grouped in to 4 sectors. Right anterior (V & VII), Left medial (IV) and left lateral with regard to portal, arterial supply and bile drainage[2].

FUNCTIONS OF LIVER[3]

1. **Formation and secretion of bile**
2. **Secretion of plasma protein**

   Albumin

   Fibrinogen

   α 1- Antitrypsin

   Ceruloplasmin

   Haptoglobins

   Transferrin

   C3 component of complement

3. **Inactivation of various substances**

   Toxins

   Steroids

   Hormones

4**. Storage function**

   Glycogen Storage

   Lipid Storage

   B_{12} and Folic acid storage

   Fat and water soluble vitamins

5. **Synthesis of Immuno globulins.**

   IgG, IgM, IgA

6. **Synthesis of Urea**

Cirrhosis of liver is characterized by irreversible chronic injury of the hepatocytes with extensive fibrosis and formation of regenerative nodules2. These features result from the hepatocytes necrosis, collapse of the supporting reticulum network with subsequent connective tissue deposition distortion of the vascular bed, and nodular regeneration of the remaining liver parenchyma.

The central event leading to hepatic fibrosis is activation of hepatic stellate cell. According to functional status of cirrhosis it may be compensated or decompensated cirrhosis.

COMPENSATED CIRRHOSIS[4]

Cirrhosis discovered at routine examination or biochemical reaction with external signs and symptoms of liver failure like nausea, vomiting, indigestion, flatulence, dyspepsia, are early features in alcoholic cirrhosis. It may be suspected in patients with vascular spiders, palmar erythema, unexplained epistaxis or edema of ankles.

Clinically firm enlargement of liver and Splenomegaly may be present. There will be a slight increase in serum transaminase or γ Glutamyl Transferase level[4].

DECOMPENSATED CIRRHOSIS

Signs of liver cell failure usually of ascites, jaundice are present in patients with Decompensated liver disease. Continuous mild fever is often due to gram negative bacteremia, continuing hepatic cell necrosis or malignant transformation. Jaundice implies liver cell destruction, exceeds the capacity for regeneration and is always serious[4].

ETIOLOGICAL CLASSIFICATION OF CIRRHOSIS[2]

1. **Alcoholic**
2. **Post necrotic or post infective HBV / HCV / HBV & HDV**

3. **Metabolic disorders**
    a. Haemochromatosis
    b. Wilson's disease
    c. Alpha 1 antitrypsin deficiency
    d. Cystic fibrosis
    e. Glycogen storage disease
    f. Galactosemia
    g. Hereditary fructose intolerance
    h. Hereditary tyrosinemia
    i. Ornithine Trans carbomylase deficiency.
    j. Abetalipoproteinemia
    k. Porphyria
4. **Biliary tract disease**
    a. Extra hepatic biliary obstruction
    b. Intra hepatic biliary obstruction
    c. Primary biliary cirrhosis
    d. Primary sclerosing cholangitis.
5. **Venous outflow obstruction**
    a. Veno occlusive disease
    b. Budd – chiari syndrome
    c. Cardiac failure
6. **Autoimmune chronic liver disease**
7. **Drugs and toxins**
8. **Other Causes**
    a. Obesity, diabetes mellitus
    b. Intestinal bypass
    c. Sarcoidosis
    d. Indian childhood cirrhosis

Clinical manifestation in chronic liver disease is due to

(i) Portal hypertension

(ii) Hepato cellular failure.

FEATURES DUE TO PORTAL HYPERTENSION[5]

Splenomegaly

Ascites

Esophageal varices

Anorectal Varies

Dilated veins over abdomen.

STIGMATA OF CHRONIC LIVER DISEASE[6]

Face

Parotid enlargement

Telengectasia

Paper money skin

Shrunken facies.

Eyes

Jaundice[7]

Loss of eye brows

Xanthelasma

Trunk & abdomen

Ascites

Spider angioma

Loss of body hair.

Hands

Pallor

Anemia

White nails

Dupuytren's contracture

Palmar erythema

Clubbing

Skin

Spider naevi[8]

Scanty body hair

Slate grey pigmentation

Scratch marks.

Purpura, bruising.

Nutrition

Muscle wasting

Glossitis

Angular Stomatitis

Anaemia

Endocrine

Gynaecomastia[9]

Testicular atrophy

Loss of Libido

ROLE OF LIVER IN HEMATOPOIESIS AND HEMOSTASIS[10]

Liver plays an important role both in hematopoiesis and hemostasis. Thrombopoietin, a regulator of platelet synthesis is secreted by liver[10,2]. Liver acts as a storage organ for vitamin B_{12} and folic acid which are necessary for the maturation of RBCS and WBCs.

Liver is one of the primary site of reticulo endothelial system, contains plenty of kupffer cells, plays an important role in immunity and secretes immunoglobulin[2].

Liver plays a key role in B_{12} metabolism in taking part in enterohepaic circulation and also secretes transcobalamin I, necessary for the transport of B_{12} to the storage site.

ROLE OF LIVER IN HEMOSTASIS

The role of liver in hemostasis is through the synthesis of Thrombopoietin, regulator of platelet production and synthesis of clotting factors. Liver is also a site of synthesis of inhibitors of coagulation cascade and also the regulator of fibrinolysis. Thus liver is a key regulator of hemostasis[11, 12].

Where the vessel is injured, three haemostatic responses are initiated. The response occur in stepwise pattern as

1. The blood vessel constricts
2. Platelets adhere at the site of damage and aggregate.
3. Fibrin clot is formed and modified.

First the blood vessel constricts, following which the platelets adhere aggregate and forms a temporary plug. It is reinforced with a fibrin clot, through a coagulation cascade. The fibrin clot is modified and after tissue healing, it is dissolved by fibrinolytic components.

CLOTTING FACTORS

Clotting factors are the key factors in coagulation cascade. The summary of coagulation cascade is shown below.

Liver is the principal site of synthesis of all the coagulation protein with the exception of vWF and factor VIII C[13]. The proteins include.

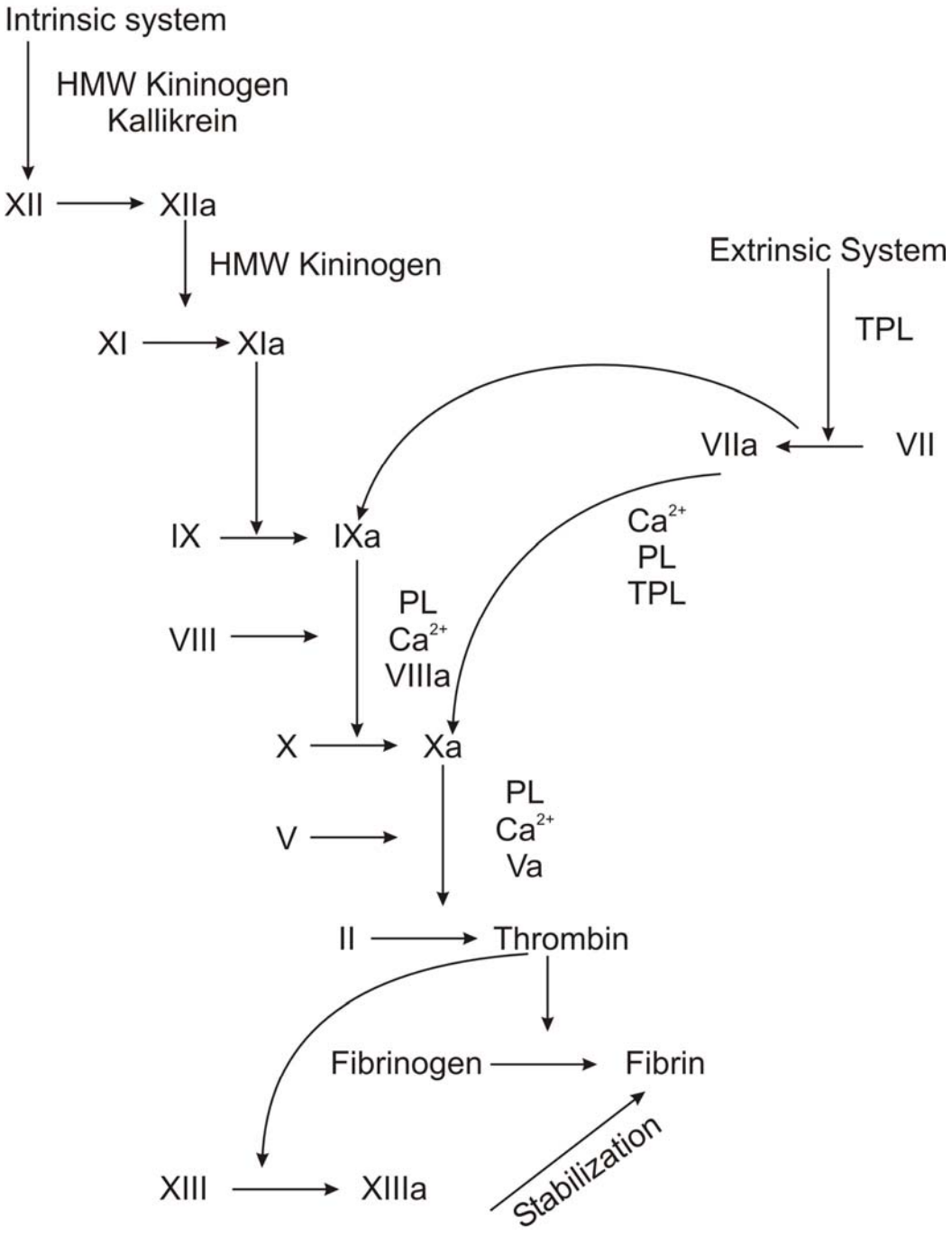
Vitamin K dependent factors – II, VII, IX & X

Labile factor – V

Contact factor XI & VII

Fibrinogen and fibrin stabilizing factors.

COAGULATION CASCADE[13]



Liver is the site of vitamin K storage. The Vitamin K is essential for the synthesis of factors II, VII, IX and X. The function of these blood clotting proteins depend on the conversion of glutamic acid residues, post ribosomally to γ carboxy glutamic acid by a carboxylase that requires vitamin K.

Inhibitors of coagulation cascade are also synthesized by the liver.

These are Antithrombin III

Protein C & S (Vitamin K dependent)

Heparin cofactor II

HEMATOLOGICAL ABNORMALITIES IN LIVER DISEASE ANAEMIA IN LIVER DISEASE[14]

Anaemia occurs in 75 % of patients with chronic liver disease. It is mostly of moderate severity and is either normochromic normocytic or moderately macrocytic in uncomplicated cirrhosis. If cirrhosis is complicated with hemorrhage or hemolysis then microcytic hypochromic anaemia can occur.

Anaemia in uncomplicated cirrhosis is due to

i. Hemodilution – due to increased plasma volume.

ii. Shortened red cell survival - hypersplenism

iii. Reduced bone marrow response to anaemia due to reduced erythropoietin level, chronic inflammation and increased level of inflammatory cytokines suppressing the bone marrow[15].

Patients with cirrhosis have low oxygen – hemoglobin affinity which increases tissue oxygen availability, leading to better tolerance of anemia.

PLASMA VOLUME

Plasma volume is frequently increased in patients with cirrhosis especially with ascites. Hypervolemia causes low peripheral hemoglobin or erythrocyte level[16].

LIVER DISEASE AND HEMATINIC METABOLISM

IRON METABOLISM

Serum iron is bound to Beta globulin transferrin which is synthesized in liver. Total iron binding capacity largely depends on the

transferrin concentration[17]. High total iron binding capacity indicates iron deficiency. Iron binding capacity is often lowered in patients with liver disease due to decreased synthesis of trasferrin. Serum transferrin receptor level is a more reliable lab index of iron deficiency in patients with liver disease.

Iron deficiency is also associated with hemorrhage and hemolysis. Iron deficiency causes microcytic hypochromic anaemia.

Low or normal serum iron concentration with a low or normal total iron binding capacity is frequently found in uncomplicated cirrhosis. In alcohol induced liver diseases, alcohol has a toxic effect and suppresses the bone marrow[18,19] but it increases the iron absorption from the GIT. Hepatic inflammation and necrosis tend to increase serum ferritin. The rise in MCV which accompanies alcohol ingestion masks the iron deficiency.

VITAMIN B12 AND FOLIC ACID METABOLISM

Intrinsic factor is required for B_{12} absorption and there is significant enterohepatic circulation. Pernicious anaemia is associated with primary biliary cirrhosis[20,21]. Alcohol inhibits B_{12} absorption,

elevated B_{12} binding capacity occurs in cirrhosis and hepatocellular carcinoma. Liver stores 5 -10 mg of vitamin B_{12} representing 50 – 90 % of body stores[2].

Liver stores of folic acid are sufficient for only 4 to 5 months[22,2]. Alcohol induced liver disease and poor nutrition results in disordered folate metabolism. Hepatic necrosis leads to increased release of folate from liver and leads to increased urinary excretion.

Altered B12 and folate metabolism causes macrocytosis.

HEMOLYTIC SYNDROMES IN LIVER DISEASE

Recticulocytosis is frequently seen in liver disease patient. Red cell life span in reduced by about 50 % in cirrhotics with, the spleen as the major site of destruction. The hemolysis may be due to

1. Hypersplenism
2. Lipid abnormalities.
3. Hemolytic anaemia is also seen in Wilson's disease and in autoimmune hepatitis (Coombs positive)[22].
4. Intracorpuscular defects such as instability of pyruvate kinase enzyme in alcoholic liver disease leads to hemolysis.

ABNORMALITIES OF RED CELL SHAPE

Microcytosis is due to Iron deficiency of various mechanisms in decompensated liver disease[23].

Macrocytosis is seen mostly in alcoholics [24,15]. The increase in MCV is due to

- Increase in RBC membrane cholesterol and phospholipid content.
- Recticulocytosis associated with hemorrhage and hemolysis.
- Abnormalities in B12 and Folic acid metabolism.
- Intrinsic abnormality in bone marrow erythropoiesis.

Target cells: bowel or saucer shaped thin macrocytes.It is seen in seen in most cases of hepato cellular failure and cholestatic jaundice. Raised bile acids inhibit LCAT. So the red cell membrane LCAT is decreased resulting in loading of membrane with cholesterol and lecithin forms target cells [25]

Acanthocytosis: Seen in severe liver disease. It is a bad prognostic indicator. Where it is associated with hemolytic anaemia it is called as spur cell anaemia[26].

Echinocytes: Speculated red cells due to changes in HDL in Liver disease patients.

TABLE: 1 ABNORMALITY OF RBCs[6]

Abnormality	**Primary liver disorders**	**Disease in other systems**
Macrocytes	Many types of liver diseases	Megaloblastic anaemia Hypothyroidism, cytotoxic drugs.
Targets cells	Many types of liver disease	Thalassaemia Other haemoglobinopathies Hyposplenism, e.g. SLE, celiac disease
Spherocytes	Zieve's syndrome	Hereditary spherocytosis Autoimmune haemolytic anaemia Burns
Echinocytes Acanthocytes	Severe chronic liver disease Very severe disease (especially alcoholic) (spur-cell anaemia)	Haemolytic anaemia Abetalipoproteinemia Anorexia nervosa / Malnutrition McLeod phenotype
Burr cells Fragmented cells (schistocytes)	Hepatorenal syndrome	Renal failure Thoromobotic thromobocytopenic purpura,Microangiopathic haemolytic anaemia, DIC, HELLP syndrome some haemoglobinopathies
Stomatocytes Tear – drop poikilocytes	Alcoholic cirrhosis	Alcoholism Haemolytic anaemias Primary and secondary myelofibrosis
Nucleated red cells punctuate basophilla	Acute fatty liver of pregnancy	Infections, e.g.malaria Heavy metal poisoning Haemolytic / dyserythropoietic anaemia.
Rouleaux Auto agglutination Sickle cells		Myeloma / macroglobulinemia / lymphoma Autoimmune haemolytic anaemia Sickle cell disease.

WBC CHANGES IN LIVER DISEASE

Leukocytosis can occur in response to associated infection, hemorrhage, hemolysis and malignancy. Eosinophilia in frequently seen in association with parasitic disease, hepatocellular carcinoma, hepatic vein thrombosis, drug induced and also in primary biliary cirrhosis.

Leucopenia seen in Liver disease patients is due to hypersplenism[27] or a toxic effect on bone marrow (alcohol). Neutrophil function is affected by disturbance in late maturation of granulocyte differentiation. Chemotaxis is inhibited. There is a low level of complement C_3

Hypergamma globulinemia is a well recognized feature of cirrhosis. It is initiated by immunization with enteric organisms normally filtered by liver. IgG and IgA are markedly increased[28]. There is generalized immunological hyperactivity. Benign monoclonal gammopathy is associated with primary biliary cirrhosis.

Specific Immunoglobulin's are

IgA – Alcoholic cirrhosis

IgM – Primary biliary cirrhosis

IgG – Auto Immune Hepatitis.

PLATELETS IN LIVER DISEASE

In decompensated liver disease patients, defects of platelet number and function are well documented. The mechanisms for thrombocytopenia are[29,30] :

1. Shortened mean platelet life span.
2. Platelet pooling in an enlarged spleen[31].
3. Inability of marrow to compensate.
4. Reduced thrombopoietin production[32].
5. Platelet associated immunoglobulin deficiency.

There is no clear relationship between the abnormalities of platelet kinetics and the severity of liver disease as very low platelet count often accompany portal hypertension and Splenomegaly in patients with relatively normal liver function.

Normal platelets enriched with cholesterol show increased aggregability by ADP and adrenaline. Platelets in liver disease tend to be cholesterol rich but their aggregability is diminished, probably because the arachidonic acid content of platelet phospholipids is reduced.

Platelets from patients with cirrhosis also exhibit a defect in vWF binding domain. A raised level of platelet associated immunoglobulin is found in patients with decompensated liver disease such as primary biliary cirrhosis, alcoholic cirrhosis, chronic active hepatitis.

HEMOSTASIS IN CHRONIC LIVER DISEASE

The abnormalities in hemostasis are due to

i. Impaired synthesis of clotting factors.
ii. Synthesis of abnormal clotting proteins.
iii. Quantitative, qualitative platelet defect
iv. Enhanced fibrinolytic activity
v. Disseminated intravascular coagulation[12].

DECREASED CLOTTING FACTOR LEVELS

Factors II, VII, IX and X are vitamin K dependent clotting factors as well as the coagulation inhibitor Proteins C & S. Factor VII is usually first to be decreased due to its short half life .The non functional precursor forms of clotting factors are called proteins induced in vitamin K. absence (PIVKA).They are produced defective carboxylation in the presence of vitamin K deficiency.

Factor V is synthesized in liver in the absence of vitamin K. Thus a decreased level of factor V associated with decreased levels of factor II, VII, IX and X is an indicator of hepatocellular insufficiency. Hypofibrinogenemia is less frequent, until there is severe liver damage. Factors XI, XII and high molecular weight kininogen are usually moderately decreased. Prekallikrein decreases early in liver disease. Factor XIII, a fibrin stabilizing factor is also decreased

DECREASED COAGULATION INHIBITORS

Protein C, S also vitamin K dependent factors and antithrombin III are decreased in hepatocellular insufficiency[34]. The deficiency is not severe and usually parallels that of factor V. The synthesis is only affected by general damage to liver. Protein C deficiency parallels the deficiency of other vitamin K dependent factors. The level of protein S remains significantly greater due to extra hepatic source of protein S.

Although levels of naturally occurring inhibitors of blood clotting are decreased in hepatocellular insufficiency clinical evidence of thrombo embolism is rarely noted. This is probably due to the balance maintained between these inhibitors and the procoagulant.

Factors VIII is usually elevated in decompensated liver disease, which reflects extra hepatic synthesis associated with decreased catabolism by the diseased liver. But there is some abnormality in vWF binding domain[35].

FIBRINOGEN AND PROTHROMBIN

Functional abnormalities of fibrinogen molecule are known as dysfibrinogenemias. Acquired dysfibrinogenemias are most often associated with Decompensated Liver disease. Defective polymerization results from an abnormal glycosylation of fibrinogen molecules[55]. An increased level of sialyl transferase has been demonstrated in liver patients with dysfibrinogenemias[36]. Impairment in fibrin formation results in prolonged thrombin time. Abnormal type of prothrorombin due to defective carboxylation in des-γ -carboxy prothrorombin which is increased in chronic active hepatitis, cirrhosis and hepatocellular carcinoma.

FIBRINOLYSIS

In decompensated Liver disease patient, Enhanced fibrinolysis is due to decreased hepatic synthesis of inhibitors α2-antiplasmin and

plasminogen activator inhibitor as well as decreased clearance of tissue type plasminogen activator.

DISSEMINATED INTRAVASCULAR COAGULATION

DIC is due to the consequence of non compensated formation of thrombin and leads to the formation of platelet thrombi and fibrin within the circulation. Thus it is associated with activation and consumption of circulating platelets and consumption of factors V, VIII, VII, II & XIII Protein C & S, antithrombin III, plasminogen and α plasmin inhibitor[37].

The release of tissue thromboplastin like material by necrotic liver had been the triggering factor for DIC in severe liver failure. Increased fibrinopeptide - A levels have been found in patients with cirrhosis and chronic hepatitis. Elevated level of thrombin - anti thrombin complexes have been reported in chronic active hepatitis, decompensated liver disease, end stage liver disease and fulminant liver failure.

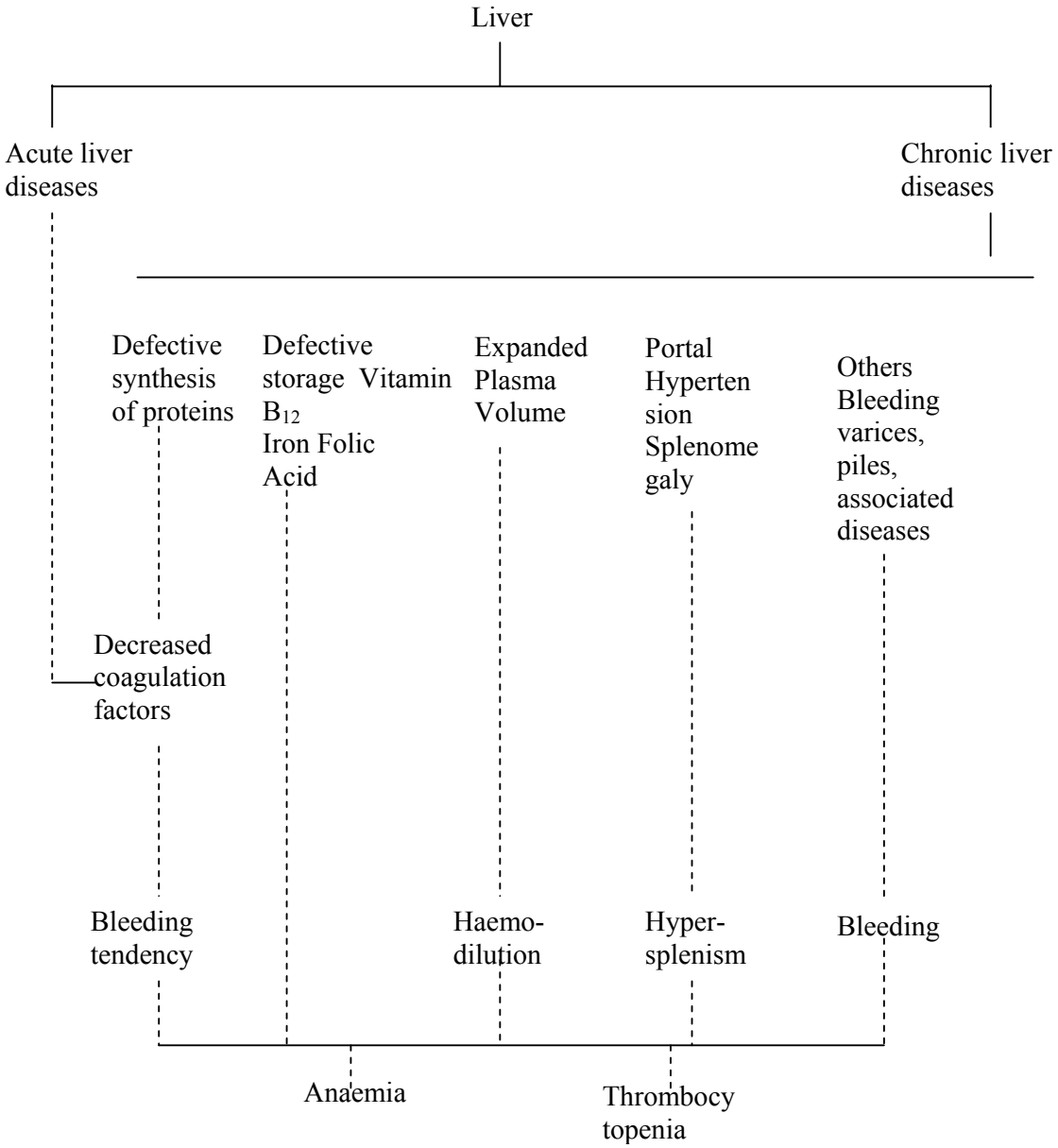
TABLE-2
COMBINATION OF HAEMATOLOGICAL ABNORMALITIES WITH[6]

ABNORMAL LIVER FUNCTION TESTS

Abnormality	Haematological indices	Primary liver disease	Disease in other systems
Red cell anaemia	Increased MCV (macrocytic)	Many liver diseases	Alcoholism Vitamin B12/folate deficiency Haemolysis (reticulocytes up)
	Low MCV/MCHC (microcytic) Normochromic Normocytic High reticulocyte count Low reticulocyte count	With iron deficiency With dilutional anaemia With hypersplenism With marrow aplasia (viral hepatitis)	Thalassaemia Anaemia of chronic disease Haemolysis Paroxysmal nocturnal haemoglobinuria (Budd-Chiari syndrome)
Normal haemoglobin Erythrocytosis	Increased MCV Low MCV	Mild liver disease With iron deficiency Hepatocellular carcinoma Viral hepatitis (rare)	Alcoholism Thalassaemia trait
White cells	Increased Neutrophils increased Lymphocytes increased Eosinophils increased	With infection. neoplasia inflammation With bacterial infection or steroid therapy Viral infections Parasitic infection Drug hepatitis Chronic active hepatitis (rare), sarcoidosis	Myeloproliferative disorder Leukemia, Lymphoma, drugs Connective tissue disorders
	Monocytes Basophils/mast cells increased		Tuberculosis, Leukemia, myeloprolifcrative disease mastocytosis
	Decreased	With infection, marrow aplasia, or hyposplcnism	Infections (typhoid, SBE, tuberculosis, septicaemia) leukemia
	Lymphocytes decreased		Viral infections
Platelets	Increased Decreased	Liver disease and Hemorrhage. neoplasia inflammation With hypersplenism. viral hepatitis	Myeloproliferativc disorder Lcukaemia/lymphoma Connective tissue disorders Paroxysmal nocturnal hacmoglobinuria

HAEMATOLOGICAL ABNORMALITIES IN DECOMPENSATED CHRONIC LIVER DISEASE[2]

The Haemotological abnormalities in chronic liver disease add morbidity to the primary pathology and increase the mortality. The possible factors summarized as.



Materials and Methods

DESIGN OF STUDY

MATERIALS AND METHODS

To assess the hematological abnormalities in chronic liver disease, the prevalence study was conducted in Coimbatore medical College Hospital during the period from Jan 2006 to June 2007. About 50 patients were selected in for this study.

All the cases included in the study were admitted in the hospital ward evaluated for chronic liver disease and the hematological abnormalities. Oral consent for the clinical examination and for the lab investigations were obtained from all patients. Written consent also obtained for the special procedure like upper GI endoscopy.

All the patients were interrogated regarding their symptoms, duration of illness, bleeding tendencies, abdominal distension, jaundice, oliguria. Past history regarding previous treatment of diabetes, hypertension, tuberculosis, coronary heart disease, trauma, blood transfusion, surgery needle pricks, contact with blood products.

Personal history regarding alcoholism, smoking, high risk behavior also got. Family history of any liver disease was also noted. Then the entire patient was subjected to general examination and systemic examination. Patients were submitted to blood investigations.

Patients were evaluated for chronic liver disease to establish the diagnosis of cirrhosis. In patients with defects in coagulation is evidenced by increased prothrombin time or decreased platelet count, had increased bleeding tendency during bone marrow biopsy.

After establishing the diagnosis patients were evaluated for hematological abnormalities. All blood investigations regarding hematological profile were done in clinical pathology laboratory in Coimbatore medical College Hospital.

Similarly prothrombin time and activated partial thromboplastin time were done at outside laboratory.

TO ASSESS RBC ABNORMALITY

1. RBC count:

RBC count was done with Neubauer's chamber using Hayem's fluid or auto analyser[13].

Normal Value:

1. Male 4- 5 to 5.9 x 10^6 mm^3
2. Female 4 to 5.2 x 10^6 mm^3

2. Hemoglobin estimation:

Done by Sahli's method, based on conversion of hemoglobin to acid hematin or acid analyzer.

Normal value:

1. Male 13.5 to 17.5 gm %
2. Female 12 to 16 gm %

3. Packed cell volume (PCV)

It was done in autoanalyser or using microhematocrit capillary method.

Normal value:

1. Male 42 to 52 %
2. Female 37 to 47 %

4. **MCV, MCHC, MCH;**

Were estimated by autoanalyser

(I) MCV = $\frac{PCV x 10}{RBC\ in\ million\ \ per\ cumm}$

80 – 97 FL – Normal

< 80- microcytic

>97 – macrocytic

(ii) MCH = $\frac{Hbx10}{RBC\ in\ million\ \ per\ cumm}(Pg)$

27 - 31 - N Normal

< 27 – Hypo chromic

> 31 - Hyper chromic

(iii) MCHC = $\frac{Hbx100}{PCV}(\%)$

32 – 36 % - Normal`

< 32 Hypo chromic

> 36 – Hyper chromic

5. Peripheral smear for blood picture

Using Leishmann's stain blood picture was examined with a lab microscope.

(I) Low power field examination:

- Quality of film
- Number, distribution and staining of WBCs
- RBCs examination

(ii) High power field examination:

Assess RBC - Size, Shape, Hemoglobin concentration

(iii) Oil immersion examination:

Assess atypical cells and inclusion bodies

6. Reticulocyte count:

Stain - 1% brilliant cresyl blue

Normal – 0.2 – 2 %

7. Bone narrow study (not conducted in 23 patients because of hemostatic abnormalities[39,40].

To assess **WBC abnormality:**

1. Total WBC count

Done by QBC method or using Neubauer's chamber with Turke's fluid .Normal 4,500-11,000 cells per cmm[17]

2. **Differential count**

Assessed by QBC method or direct staining and visualizing with lab microscope.

III. to Assess hemostasis

1. Platelet count

Manually was done by Rees Eecker method (staining with brilliant cresyl blue dye or by auto analyzer).

Normal 1.5 to 3.5 x 10^5 / mm^3

2. Prothrombin time:

Done by Quick one stage method. Normal (10 – 14 sec).

3. Bleeding time – By Ivy's method- Normal (1-7 mts)

4. Clotting time by lee & white method – Normal (5 -15 min)

Activated partial thromboplastin time Normal (24 – 34 sec).

IV. Liver function test

In fifty cases, the following biochemical investigations were carried out to prove the presence and assess the severity of hepatocellular failure.

1. Serum Proteins — Total — Albumin
   Differential — Globulin
2. Serum billirubin — Total — Conjugated
   Differential — Unconjugated
3. Serum Alkaline phosphatase
4. AST and ALT.

V. UPPER GI ENDOSCOPY

UGI endoscopy was done at the medical gastroenterology department, after obtaining patient's written consent. Patient was explained about the procedure, side effects. Patients were kept on over night fasting. Upper GI endoscopy was correlated with other finding to establish the diagnosis.

INCLUSION CRITERIA

1. Adult patients presenting with signs and symptoms of chronic liver disease.

EXCLUSION CRITERIA

1. Acute liver cell failure
2. Patients with known GIT malignancy or known primary hepatocellular carcinoma.
3. Patients with primary coagulation disorder,
4. Liver cell failure due to infective cause like septicemia or end toxemia.

Observation and Results

DATA ANALYSIS

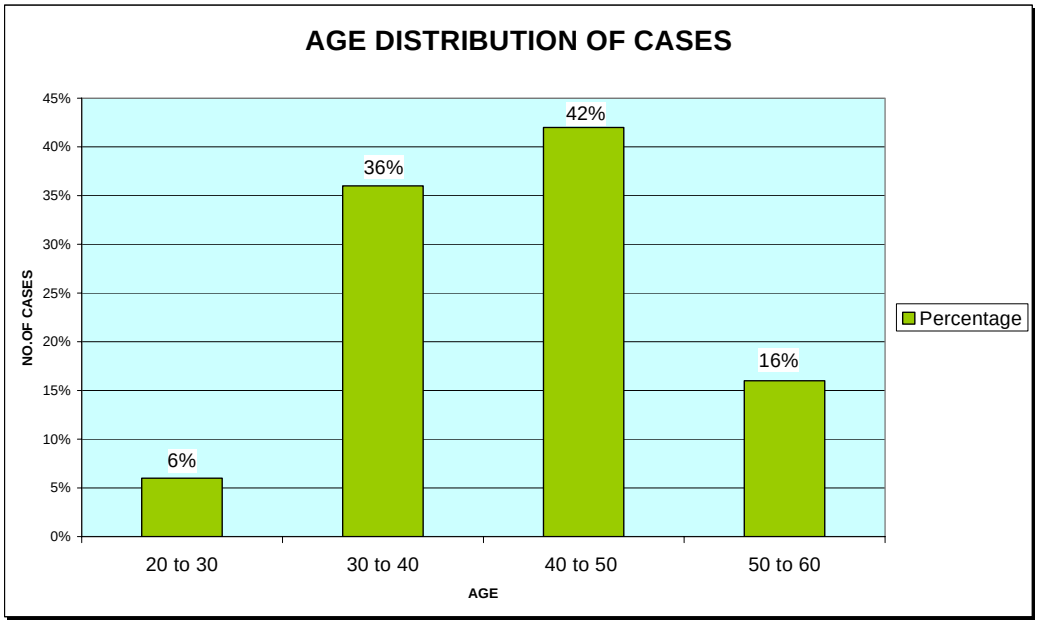
This study regarding assessment of hematological profile and hemostasis was conducted among 50 inpatients in medicine department at Coimbatore Medical College Hospital.

Out of 50 patients is this study, there are 40 male patients and 10 female patients. The age of patients in this study was in the range from 20 to 60.

Table 3: Age of Patients

Age in Yrs	Male	Female	Total	Percentage
20 to 30	2	1	3	6 %
30 to 40	13	5	18	36 %
40 to 50	18	3	21	42 %
50 to 60	7	1	8	16 %

Most of the patients in the study were in the middle age group and only 6% were in younger age. Out of 3 patients one patient was diagnosed to have Wilson's disease and others were of unknown etiology. Remaining 47 patients were diagnosed as chronic decompensated liver disease with pathology as cirrhosis and were of variable etiology.



ALCOHOLISM

Among 10 female patients, none gave history of alcoholism and among the 40 male patients 31 patients were found to be alcoholics.

PAST HISTORY OF JAUNDICE

Among 50 patients only 16 patients had past history of jaundice. Later serologic investigations for HBV Ag. Anti HCV antibody showed 6 patients positive for HBS Ag and only one shows positive for anti HCV antibody.

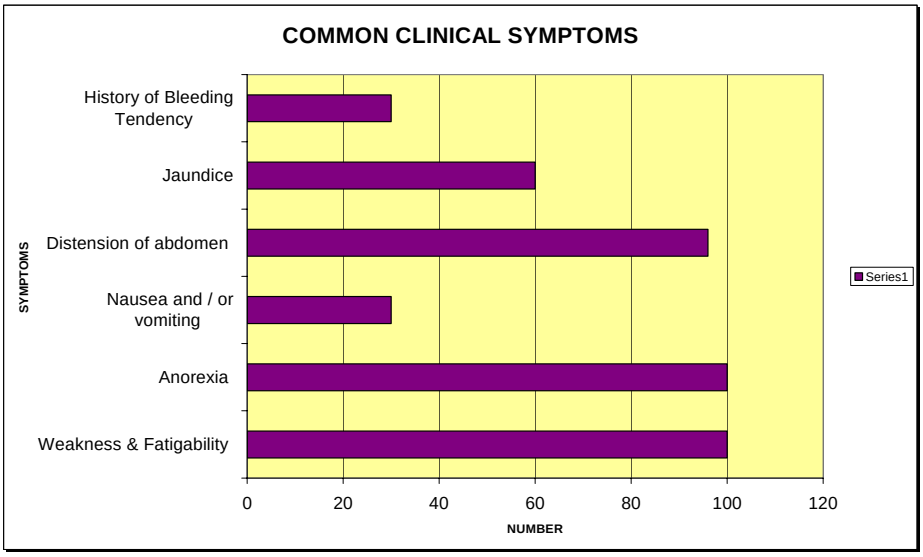
While coming to data analysis of investigations, among the 50 Chronic Liver Disease patient's only 43 patients has raised billirubin level. About 7% of the patients were with normal billirubin level.

ANALYSIS OF SYMPTOMS AND SIGNS

TABLE - 4

No.	Symptom	No. of cases	%
1.	Weakness & Fatiguability	50	100
2.	Anorexia	50	100
3.	Nausea and / or vomiting	15	30
4.	Distension of abdomen	48	96
5.	Jaundice	30	60
6.	History of Bleeding Tendency	15	30

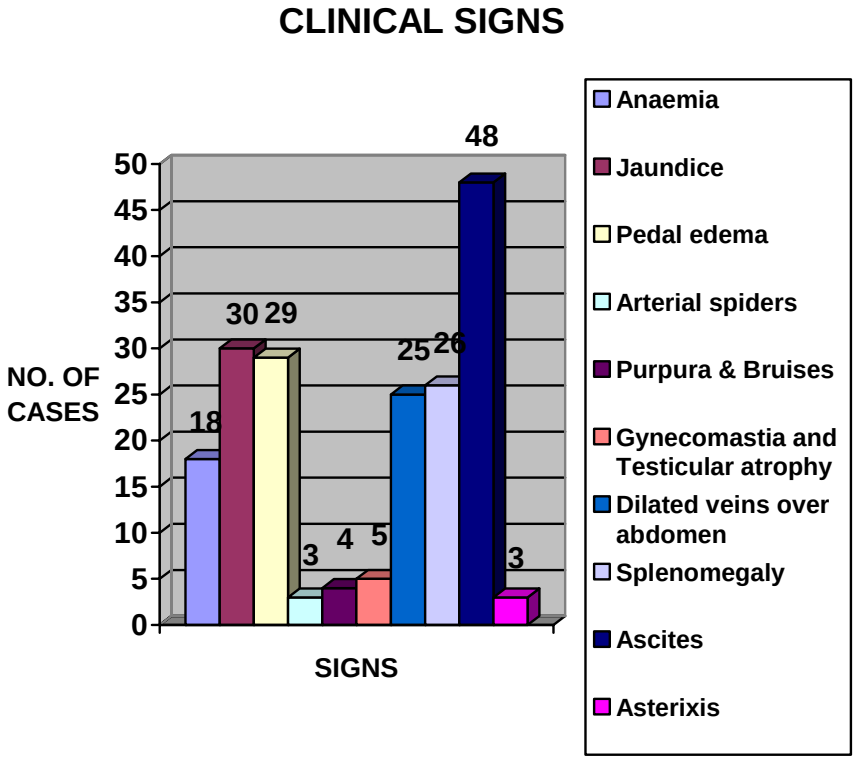
Among the 50 patients 100 % had anorexia and weakness Fatigability. Jaundice was found in 60 %. Bleeding tendency was observed in 30 % of them.



ANALYSIS OF SIGNS:

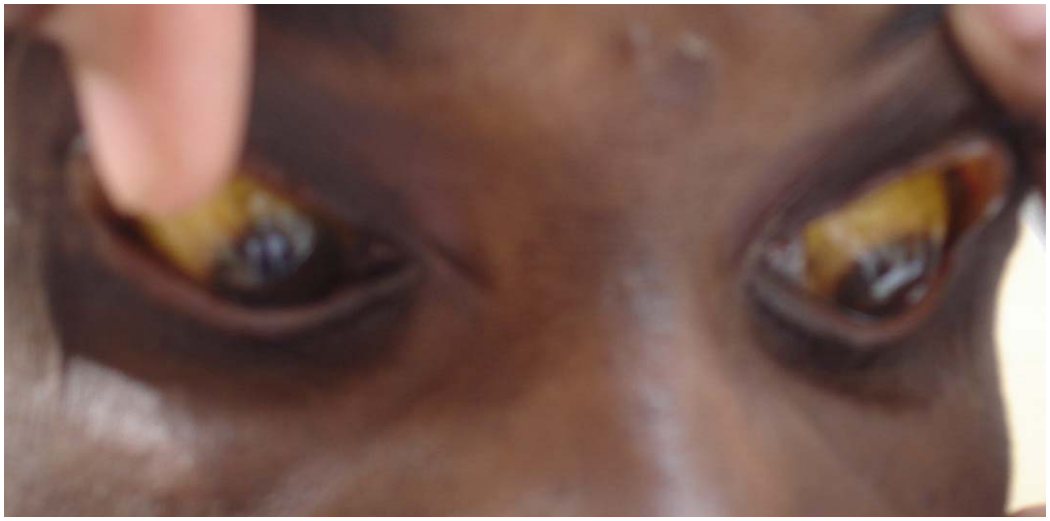
TABLE - 5

No.	SIGNS	No. of cases	%
1.	Anaemia	18	36
2.	Jaundice	30	60
3.	Pedal edema	29	58
4.	Arterial spiders	3	6
5.	Purpura & Bruises	4	8
6.	Gynecomastia and Testicular atrophy	5	10
7.	Dilated veins over abdomen	25	50
8.	Splenomegaly	26	52
9.	Ascites	48	96
10.	Asterixis	3	6



Among the 50 patients 60 % had Jaundice and 36% had anemia. Splenomegaly observed in 52 %. Spiders and Asterixis are observed 3 patients.

SIGNS OF LIVER CELL FAILURE

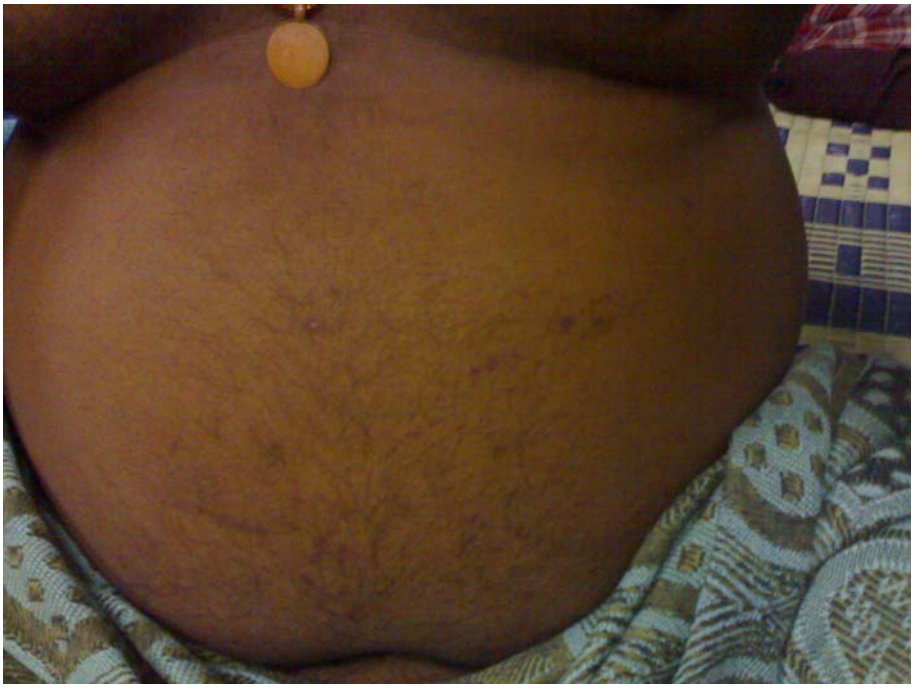


JAUNDICE

ASCITES WITH DILATED VEINS

SIGNS OF LIVER CELL FAILURE

ALOPECIA



PURPURA

PURPURA

ANALYSIS OF RBCS

Patients in the study were analysed for the presence and absence of Anaemia and the characteristics of anaemia when present.

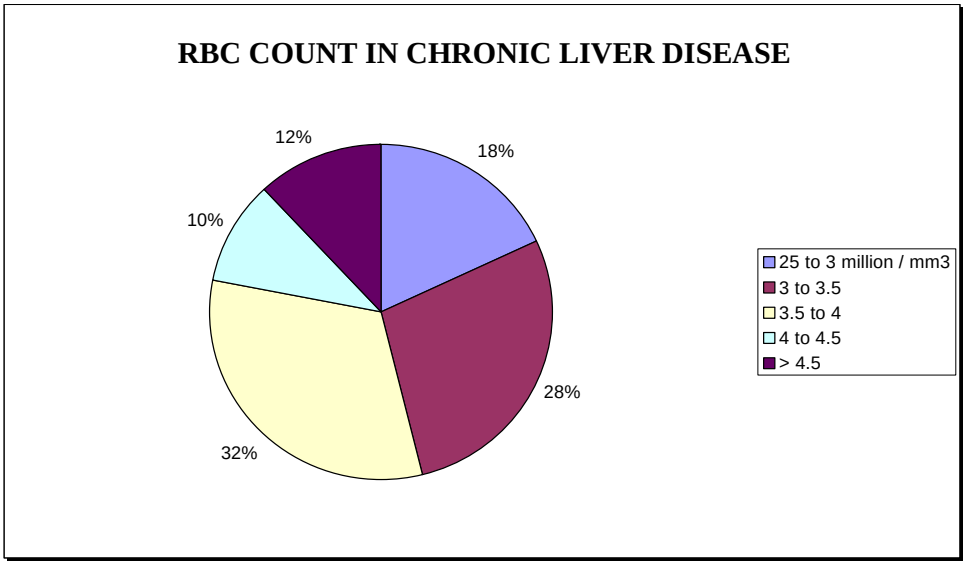
44 patients had anaemia and only six patients had normal hemoglobin above 12 gm%. About sixteen patients had severe anaemia less than 8 gm%.

Table 6 ANEMIA IN CHRONIC LIVER DISEASE

Haemoglobin gm %	Cases	Percentage
< 6	2	2 %
6 to 8	14	28 %
8.1 to 10	22	44 %
10.1 to 12	6	12 %
12.1 to 18	6	12 %
> 14	Nil	

Table 7 RBC COUNT IN CHRONIC LIVER DISEASE

RBC Count	Cases	Percentage
25 to 3 million / mm3	9	18 %
3 to 3.5	14	28 %
3.5 to 4	16	32 %
4 to 4.5	5	10 %
> 4.5	6	12 %

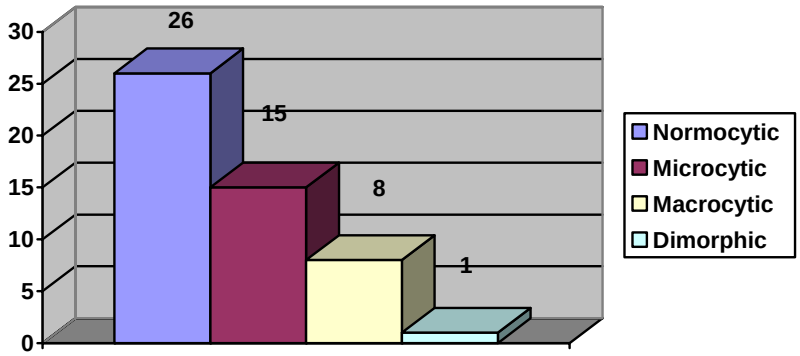


CHARACTERISTICS OF ANAEMIA

All the twelve patients with normal hemoglobin level had normochromic and normocytic blood picture. Among the 50 patients 26 patients had normochromic and normocytic anaemia, 15 patients had microcytic anaemia and 8 patients had macrocytosis. Only one had dimorphic anaemia, patients with microcytic anaemia showed anisocytosis. And poikilocytosis**. Target cells** were seen in only two patients. **Acanthocytes** was not seen in any of the peripheral smears. Patients with macrocytosis had meant corpuscular volume more than 97 fl.

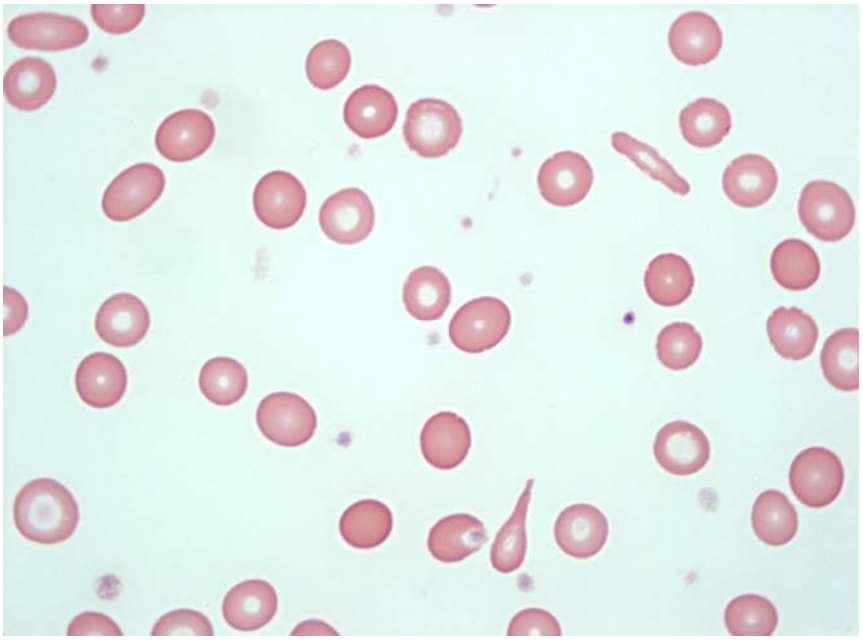
Table 8 Type of Anaemia

Type of RBCs	Patients with anaemia	Percentage
Normocytic	26	52 %
Microcytic	15	30 %
Macrocytic	8	16 %
Dimorphic	1	2 %

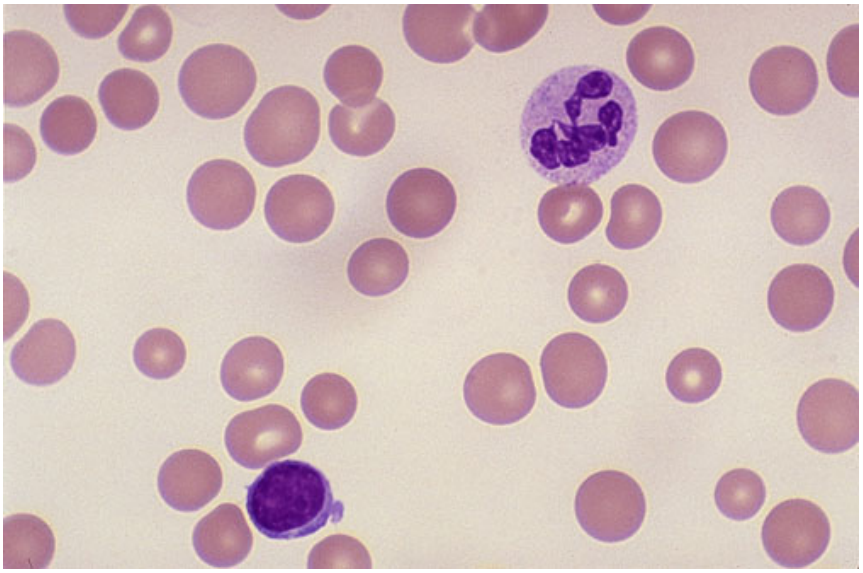


TYPE OF ANAEMIA

BLOOD PICTURE

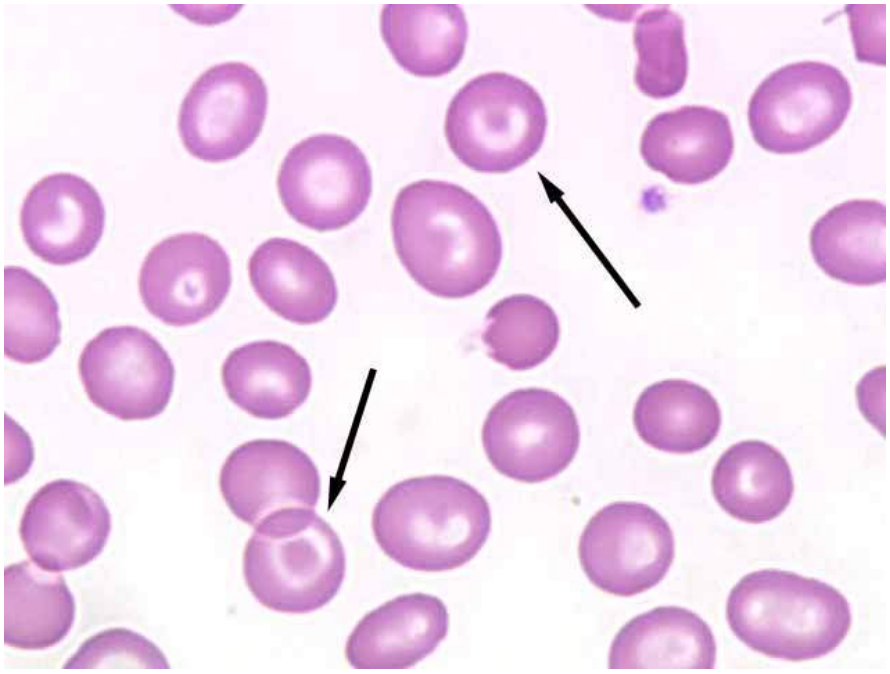


MICROCYTIC HYPOCHROMIC ANAEMIA

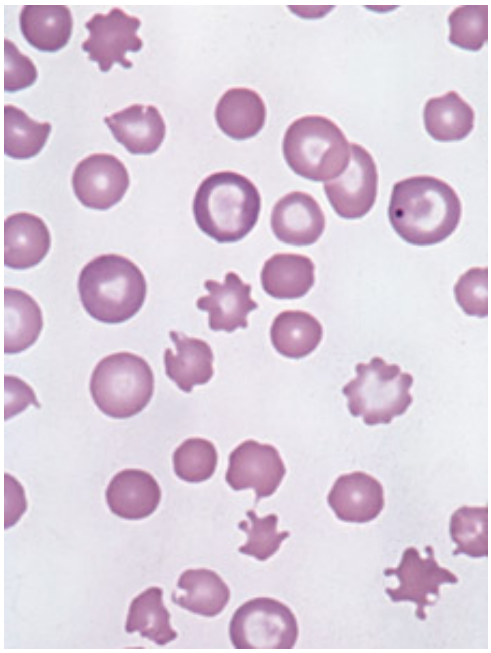


MACROCYTOSIS WITH HYPERSEGMENTED NEUTROPHILS

BLOOD PICTURE



TARGET CELLS



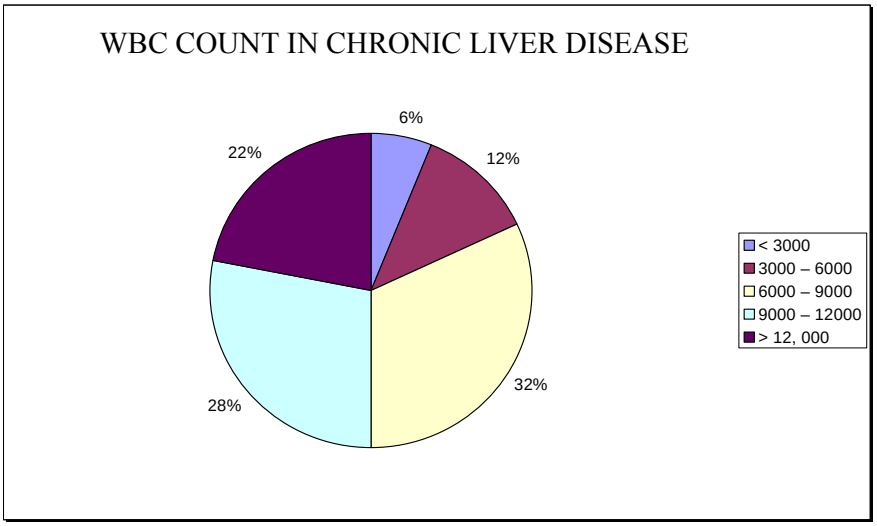
ACANTHOCYTES

WBC ABNORMALITIES

The analysis of WBCs was done with the total count and the differential count. The total count of WBCs range from 1050 / mm^3 to 16,100/mm^3. Among the 50 patients Leukocytosis were observed in 11 patients. Eosinophilia was found in one patient. Leukocytosis were observed in patients with fever due to secondary infection of Ascites due to repeated paracentesis and four patients had Leukocytosis due to spontaneous bacterial peritonitis. Leucopenia was present in 6% of patients. Lymphocytosis seen in 12 % of patients, Eosinophilia in 2 % of patients.

Table 9 WBC COUNT IN CHRONIC LIVER DISEASE

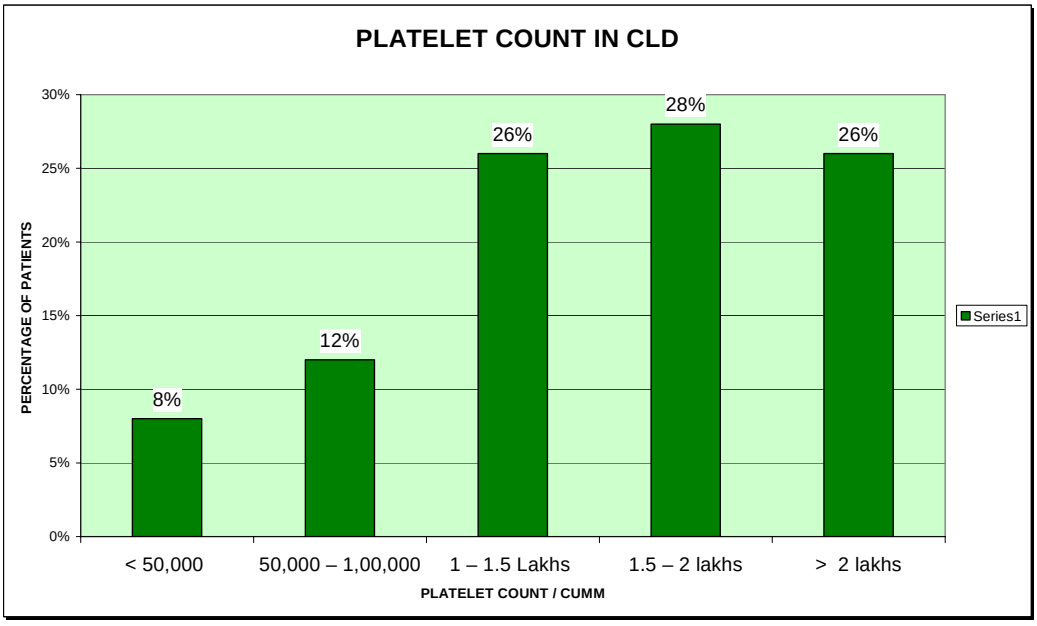
Total count in Cells / mm3	No. of patients	Percentage
< 3000	3	6 %
3000 – 6000	6	12 %
6000 – 9000	16	32 %
9000 – 12000	14	28 %
12, 000	11	22 %



PLATELET ABNORMALITIES

Table 10 Platelet Count in Chronic Liver Disease

Total count in Cells / mm3	No. of patients	Percentage
< 50,000	4	8%
50,000 – 1,00,000	6	12 %
1 – 1.5 Lakhs	13	26 %
1.5 – 2 lakhs	14	28 %
> 2 lakhs	13	26 %



Thrombocytopenia was found in 23 patients among 50 cases is the study. Severe thrombocytopenia of < 50,000 cell / mm^3 was found in patients with large spleen >8 cms and had a history of massive hemetemesis. Thrombocytopenia was associated with history of atleast an episode of hematemesis. Among the patients with severe thrombocytopenia 3 patients were found to have disseminated intravascular coagulation, later confirmed by the raised value of APTT and PT.

Among the patients with normal level of platelets about 6 patients had history of atleast on episode of hematemesis. Among the 27 patients with normal platelet levels about 11 patients had mild Splenomegaly and 6 patients had moderate Splenomegaly. In 5 patients Splenomegaly was observed in Ultra Sonogram only.

SERUM PROTEINS

Patients were analysed for the estimation of serum proteins, which is the synthetic function of the liver and evaluated for albumin globulin ratio which will be altered in the chronic liver disease patients.

TABLE - 11: SERUM PROTEINS IN Chronic Liver Disease

Total proteins gm%	No of patients	Percentage
>6	7	14%
6 to 5	21	42%
5 to 4	21	42%
<4	1	2 %

Among patients only 14% had total proteins more than 6 gm% and only one patient had total protein <4 gm% and others in the middle group. 42% had protein in the range of 6-5 gm% and 4% had 5-4 gm% proteins range. All the patients had albumin globulin ratio reversal, which is again, favours the diagnosis of Chronic Liver Disease.

ABNORMALITIES IN COAGULATION

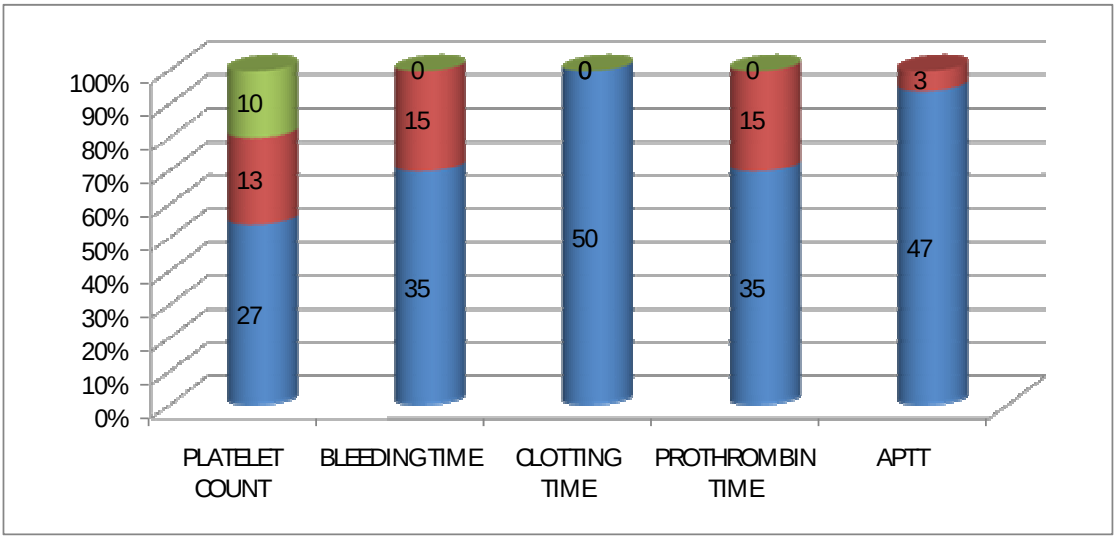
The liver secretes all the clotting factor except factor VIII and VWF, As we had no facility for the estimation of individual clotting factors, the patients were assessed for the coagulation profile by testing for prothrombin time and activated partial thromboplastin time. Among the 50 patients 15 patients had prolonged prothrombin time and 35 patients had normal prothrombin time. There was no correlation between the severity of jaundice and the prolongation of prothrombin time.

Among the 15 patients with prolonged prothrombin time about 8 patients had history of atleast one episode of hemetemesis. Bleeding time was

TABLE – 12 - HEMOSTATIC PARAMETERS

No	Type of change		No. of cases	%
1.	**Platelet Count**			
	Normal (>1.5 lakhs)		27	54 %
	Low normal (1-1.5 lakhs)		13	26 %
	low (< 1 lakhs)		10	20 %
2.	**Bleeding time**		35	70 %
	(1-7 mts)	Normal	35	70 %
		Prolonged	15	30 %
3	**Clotting time**			
	(<15 mts)	Normal	50	100 %
		Prolonged	0	0.0
4	**Prothrombin time**			
	(10-14 sec.)	Normal	35	70 %
		Prolonged	15	30 %
5.	**APTT (24-34 sec)**	Normal	47	94 %
		Prolonged	3	6 %

HEMOSTATIC PARAMETERS



Prolonged in 10 patients who had platelet counts less than 1,00,000 / mm^3 Bone marrow study was not done with the patients with low platelet count and prolonged prothromboin time due to the risk of increased bleeding.

Among the 50 patients APTT prolonged in 3 patients. It was significantly raised in patients with DIC. They had history of spontaneous bleeding with internal bleeding and signs of endotoxemia. All the three had severe thrombocytopenia with platelets < 50,000 / mm^3

Bone marrow biopsy was done in all patients except those patients who had abnormal coagulation profile. Most of patients had normocellular bone marrow and 22% patients had hyper cellularity. There was no hypoplasia and aplastic changes.

Discussion

DISCUSSION

The study involving 50 patients done at Coimbatore Medical College Hospital has thrown light over the hematological abnormalities of chronic liver disease. The results of this study confirms with previous published reports.

RBC ABNORMALITIES

In the study we inferred that 88 % of the total patients had anemia and among them 32 % of cases had severe anemia.

According to studies by Kimber C, Deller DJ and Lander H[41]. The mechanism of anemia in Chronic Liver Disease 1965 and sheehy w and Berman A, anemia occurs in upto 75 % of patients with chronic liver disease. It is characteristically of moderate severity and is either normochromic normocytic or moderately macrocytic.

In our study 32% patient had severe anemia less than eight gm per cent. In uncomplicated cirrhosis it is rare to have such low level of hemoglobin as anemia in cirrhosis mostly due to.

I. Hemodilution

II. Decreased erythropoietin level as per the study Siciliano Hepatol 1995 who showed decreased erythropoietin level in cirrhosis patients with anemia when compared with patients with hypochromic anemia due to iron deficiency.

Cirrhosis without anemia is not associated with low erythropoietin levels (Pirsi, J Hepatol 1994)[42].

3. Chronic inflammation in cirrhosis suppresses the bone marrow.

Anaemia state is further worsened by accompanying

1. Bleeding esophageal varies.
2. Bleeding peptic ulcer.
3. Malignancy
4. Bleeding anorectic varies.

In developing countries like India, people with poor socio economic state already will have nutritional anemia due to iron deficiency and B_{12} and folic acid deficiency, which is superimposed with cirrhosis leading to severe anemia. Female patients had a greater proportion of severe anemia when compared with males. It shows the poor nutritional status of women in developing countries.

Transferrin is the iron transport protein[43]. The plasma is more than 90 % saturated with iron in patients with untreated idiopathic hemochromatisis. Reduced values may be found with cirrhosis.

SERUM PROTEINS

As per Tavill AS study fall in protein concentration usually reflect decreased hepatic synthesis[44]. In our study 86 % of cases had decreased albumin and total protein level and all the 100% patients had albumin globulin ratio reversed. The hypoproteinemia was also contributed by poor socio economic status of the patients who got admitted at the government hospitals.

The mechanism for the low albumin level in cirrhosis is due to decreased synthetic function of liver. In cirrhosis there is a chronic inflammatory[4] process in progression which causes elevated cytokines level such as IL-1, IL-6, TNF-α inhibits the synthesis of albumin and transferrin . About 10 gm of albumin is synthesized by normal liver, where as with cirrhosis it synthesis only about 4 gms.

CHARACTERISTICS OF ANEMIA

According to James Dooley, Most common anemia seen in cirrhotic patients is normochromic and normocytic anemia[2].

In our study most common anemia is normocytic, normochromic. The incidence of normochromic normocytic anemia in our patients is 52 %. Where as in some studies there are varied results.

According to study done by Malhotra[45], 1951, the incidence of normocytic, normochromic anaemia was 90 %. In studies done by Bhatia (1961) and Mishra ET. al., (1982), the incidence were 59 % and 79 % respectively.

In some studies such as Kimber C. ET. al., reported 43 % of macrocytosis, which was supported also by the study by Bingham et al.

MACROCYTOSIS

The incidence of macrocytosis in our patients was 16% macrocytosis in cirrhosis is mostly due to the toxic effect of alcohol on RBC production in the bone marrow and deficiency of B_{12} and folic acid[46]. Folic acid deficiency is also exacerbated with alcohol[47] which was confirmed by the study done by Weir, Biochem, Pham 1985, and Lindenbaum[48].

MICROCYTOSIS

About 30% patients in our group had microcytic hypo chromic anemia Bleeding from esophagi is, peptic ulceration or esophageal varies, compounded by the haemostatic defects of chronic liver disease, occurs in upto 70% of patients with Liver disease as per the study conducted by Kimber, Philips, et al., macrocytosis in cirrhosis is due to :

i. Decreased total iron concentration with alterations in iron metabolism due to decreased to serum transferrin.

ii. Hemolytic due to hypersplenism, autoimmune process, Lipid abnormalities or intra corpuscular defects.

The Total Iron binding capacity BC is often lowered in cirrhosis due to reduced hepatic synthesis of transferrin.

ABNORMALITIES OF WBCs

In our study group all the 50 patients WBC total count are in the range of 1000-16,000 cell per mm^3. About 11 patients had Leukocytosis which was mostly due to infections due to community acquired infections, nosocomial infection, spontaneous bacterial peritonitis and secondary peritonitis due to repeated peritoneal paracentesis.

In our study group in patients with Leukocytosis >12,000 / mm^3 of blood most of the patients had history of repeated hospital admissions

and had repeated paracentesis. About 50 % of patients with Leukocytosis and high grade fever and all patients with Leukocytosis had increased cell count mostly of polymorphs in ascetic fluid analysis, which suggests the presence of peritonitis in this group of patients. Spontaneous bacterial peritonitis is one of the important causes of Leucocytosis[17].

Leucopenia present in 6 % of the patients may be due to

i. Direct influences of alcohol on bone marrow.
ii. Chronic inflammatory cytokines having suppressor effect on bone marrow.
iii. Hyposplenism
iv. Infection.

Eosinophilia is seen in association with parasitic disease and also associated with Hepatic vein thrombosis, hepatocellular carcinoma, and drug allergy and graft rejection. It is also found in primary biliary cirrhosis. Serum Eosinophilia cationic protein was high in patients with primary biliary cirrhosis. Eosinophilia is present in 2% of cases in our study group mostly due to parasitic infection.

IMMUNOGLOBULINS AND LIVER DISEASE

As per the studies Feizi Gut 1968 and Jensen Arch Int Med. 1982[49] and Jensen Arch Int Med. 1982 it has been proved that Hyperglobulinemia is a well recognized features of cirrhosis. It has been suggested that this polyclonal hypergamaglobulinemia is initiated by immunization with enteric organisms normally filtered by the Liver.

Cirrhosis may be associated with a state generalized hyperactivity, perhaps as a result of a defect of immune regulation. Peripheral blood mononuclear cells from cirrhosis with hypergamaglobulinemia had a normal proportion of B cells but that IgG and IgA hypergamaglobulinemia synthesis was markedly increased.

In our study almost all patients had hypergamaglobulinemia and all the 100 % cases had albumin globulin ratio reversal. The ratio reversal is also contributed by lower albumin concentration due to decreased synthesis.

PLATELETS ABNORMALITIES

Defects of platelet number and function are well documented in patients with chronic liver disease contributing significantly to their hemostatic abnormalities. Alcoholic liver disease is associated with

additional abnormalities which are probably a consequence of the toxic effect of alcohol on platelet production and function as proved by the studies by Mikhandes BMJ, 1986, Hilbom BMJ 1987[50].

Causes for thrombocytopenia are :

i. Shortened life span

ii. Platelet pooling in an enlarged spleen[51]

iii. Inability of bone marrow to compensate

iv. Reduced thrombopoietin level

In our study the above findings are evident and out of 50 patients 10 patients had thrombocytopenia < 1,00,000 / mm3 and 13 patients had mild thrombocytopenia(1 – 1.5 lakhs / mm3). All the patients with count less than one lakhs had history of bleeding tendencies and among them two patients were diagnosed to have DIC, which also contributed to the very low platelet count in cirrhotic. All the patients with platelet count less than one lakhs had increased bleeding time.

ABNORMALITIES IN HEMOSTASIS

Liver plays a major role in regulating hemostasis, synthesizing most of the clotting factors and coagulation inhibitors[52, 56], as well as some proteins of the fibrinolytic activated enzymes of the clotting and of the fibrinolytic system[57, 58].

The contributing factors are

1. Defective synthesis of coagulation factors
2. Thrombocytopenia
3. Increased fibrinolytic activity
4. Intravascular coagulation.

As per the studies Manner Ej, 1992 and Colman RW and Rubies R.N. blood coagulation 1988[53], clotting factors may be decreased even before any other evidence of liver damage[54, 59]. In hepatic cellular failure factor VII is earlier to be decreased due to its short half life then followed by factors II and X. Factor IX is usually the last to be affected.

These are vitamins K dependant proteins synthesized in Liver. If these deficiencies are unresponsive to parenteral administration of vitamin K, it can be assumed that the hepatic synthesis of clotting factors is impaired.

PROTHROMBIN TIME ABNORMALITIES

In our study 15 patients had elevated prothrombin value which is evidence of clotting factor deficiency. They were treated with vitamin K injection for a period of one week and the prothrombin time was repeated. Some showed decrease in the prothrombin value

APTT ABNORMAILITY

APTT is prolonged in all coagulation defects including platelet activity and thromoboplastin. Prolonged APTT is found in to:

1. Vitamin K deficiency
2. Liver disease[55]
3. Presence of circulating anticoagulants.
4. Disseminated Intra vascular coagulation

In our study three patients had DIC and they had significant prolongation in APTT along with increased PT with severe thrombocytopenia. Other patients with history of bleeding tendencies were found to have moderately increased APTT.

According to James Dooley APTT may be found to be moderate to highly prolonged according to the degree of liver failure[2]. In case of moderate deficiencies of factor II, IX, X and V, associated with a high level of factor VIII and APTT will be normal.[60]

DISSEMINATED INTRAVASCULAR COAGULATION

In our study 3 patients were found to have DIC and it was confirmed with prologation of PT and APTT along with severe thrombocytopenia and was confirmed by estimation of D-dimer. These

patients were found to have septicemia, and they are culture positive showing gram negative organisms.

Thus with the above studies we inferred that many of the haematological abnormalities are to be noticed in a chronic liver disease patient, so that the co morbidity which may reduce the mortality

From the above study we noted that the presence of severe anemia does not correlate with severity of disease as evident by normal serum billirubin and hypoalbuminemia. Instead it is related with history of bleeding tendency.

The character of anemia depends upon the various factors such as bleeding tendencies, dietary deficiency, alcoholism, But normochromic normocytic anemia is most commonly found and mostly due to the primary pathology like hemodilution and chronic inflammation suppressing the bone marrow. The Leukocytosis is associated with infections mostly of secondary peritonitis due to repeated paracentesis and spontaneous bacterial peritonitis.

Platelet abnormalities as assessed by Thrombocytopenia and increased bleeding time had no correlation with the severity of liver cell failure best associated in patients with large spleen and is more common in patients with bleeding tendencies.

Similarly prothrombin time and APTT are prolonged. This is correlated with the liver disease and there is significant rise in APTT along with severe thrombocytopenia is seen in patients with DIC.

Summary

SUMMARY

50 patients of decompensated chronic liver disease patients were studied.

1. Almost 80% of the patients had anemia in any one of the form.
2. Most common anaemia in cirrhosis is normochromic normocytic anemia as inferred from the study (52 %).
3. Microcytic anaemia is found in 30% of studied population
4. Macrocytosis (16%) is almost common with alcoholics.
5. Abnormal red cells such as microcytic, microcytic, target cells, anisocytosis are found to be common in cirrhosis.
6. Leucopenia (6%) is found to be rare as per the study and Leukocytosis is more common in patients with spontaneous bacterial peritonitis and secondary peritonitis.
7. Thrombocytopenia is present is more than 30% of patients and is commonly present in the patients with Splenomegaly and with the history of bleeding tendencies.
8. Prothrombin time prolonged in 46% of the patients. A significant rise in APTT with severe thrombocytopenia is found is DIC patients.

Conclusion

CONCLUSION

1. The most common anemia in cirrhotics is normochromic normocytic anemia. Microcytosis occur in patients with bleeding tendencies and macrocytosis occurs mostly in alcoholics.

2. Leucopenia occurs in a small fraction of patients and Leukocytosis occurs in patients with history of repeated paracentesis and peritonitis. Eosinophilia is associated with parasitic infections.

3. Thrombocytopenia is present in most of the cirrhosis patients and is associated with increased bleeding tendencies.

4. Increased prothrombin time and APTT due to decreased synthesis of clotting factors.

5. All the cirrhosis patients must be evaluated for hematological and haemostatic abnormalities. Early treatment to correct these co morbidities can decrease the mortality.

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Appendix

Proforma

PROFORMA

Name : Age : Sex :
IP No : Occupation : D.O.A :
D. O.D :

Presenting Compliants of :
History of Present Illness :

Nausea / Anorexia

Vomiting

Haematemesis / Malena

Swelling of Legs / Oliguria

Jaundice / Abd. pain

Loss of Wt / Appetite

Past History :

Jaundice Blood Transfusion Surgery

TB Diabetes Needle Prick GI Bleed

Personal History:

Smoking Alcohols Other

Family History :

General Examination

Anemia Jaundice

Pedal Edema Lymphadenopathy

Pulse rate BP Signs of Liver Cell failure

Examination of the Abdomen

Inspection

Palpation

Percussion

Auscultation

Examination of other systems

CVS RS CNS

Investigations

1. Hematological

RBC	MCH	Peripheral Smear
Hb	MCHC	
TLC	MCV	
DLC	PCV	

2. Liver Function Test

Serum Bilirubin – Total / Direct / indirect

Serum Protein – Total Albumin Globulin

SGOT/ PT

Alkaline Phosphatase

Ascitic Fluid Analysis – Cell count / Bio chemical

3. Coagulation profile

BT	PT
PT	APTT

4. Bone marrow study

5. Ultrasonogram Abdomen

6. Upper GI Endoscopy

7. Other Investigations

Blood Sugar / Urea

Serum Creatinine

Urine Albumin/ Sugar/ Deposit

Master Chart

ABBREVIATIONS IN MASTER CHART

BT	-	Bleeding Time
CT	-	Clotting Time
PT	-	Prothrombin Time
APTT	-	Activated Partial thromoboplastin time
MCH	-	Mean Corpuscular Hemoglobin
MCHC	-	Mean Corpuscular Hemoglobin Concentration
MCV	-	Mean Corpuscular Volume
PCV	-	Packed cell volume
UGD	-	Upper Gastro duodenal Endoscopy
LFT	-	Liver function test
AST	-	Aspartate transaminase
ALT	-	Alanine transminase
SAP	-	Serum Alkaline Phosphatase
M	-	Male
F	-	Female
+	-	Present
-	-	Absent
T	-	Total
A	-	Albumin
G	-	Globulin
D	-	Direct
I	-	Indirect
Mod	-	Moderate

S.No.	Age	Sex	IP No.	Symptoms						SIGNS									UGD Scopy varices
				Weakness & Fatigue	Anorexia	Nausea / Vomiting	Distention of abdomen	Jaundice	Bleeding Tendency	Anaemia	Jaundice	Pedal Edema	Skin	Asterixis	Gynecomastia	Veinsover abdomen	Ascities	Splenomegaly	
1	49	M	16147	+	+	+	+	+	+	-	+	+	Spider +	-	-	+	Gross	moderate	+
2	29	F	16240	+	+	+	+	+	+	-	+	+	-	-	+	-	Gross	moderate	+
3	47	M	16335	+	+	-	+	-	-	-	-	+	+	-	-	+	mild	mild	-
4	4	M	17175	+	+	-	+	+	+	+	+	+		-	-	+	Gross	moderate	+
5	51	M	17249	+	+	-	+	+	-	-	+	+	-	-	-	+	moderate	moderate	-
6	39	M	17487	+	+	-	+	+	-	+	+	+	Purpura spider	+	-	-	Mild	moderate	-
7	48	M	19248	+	+	-	-	-	+	-	-	-	-	-	-	-	mild	Normal	+
8	34	M	20140	+	+	-	+	+	-	-	+	+		-	-	+	moderate	mild	-
9	55	M	21530	+	+	+	+	+	+	-	+	+	+	-	-	-	mild	moderate	+
10	36	F	23537	+	+	-	+	+	+	+	+	-		-	-	-	mild	moderate	+
11	27	M	24148	+	+	-	+	-	-	-	-	-	-	-	-	-	mild	Normal	-
12	45	M	26670	+	+	+	+	+	-	+	+	-		-	-	+	mild	moderate	-
13	38	M	27418	+	+	+	+	+	+	+	+	+	-	+	+	+	moderate	Massive	+
14	38	M	29811	+	+	+	+	-	-	-	-	-		-	-	+	mild	mild	-
15	48	M	30611	+	+	-	+	+	-	-	+	+	-	-	-	+	mild	moderate	-
16	33	M	31145	+	+	+	+	+	+	-	+	+		-	-	+	Mild	moderate	+
17	37	M	33371	+	+	-	+	-	-	-	-	+	-	-	-	-	mild	moderate	-

S.No.	Age	Sex	IP No.	COMPLETE HAEMOGRAM									Peripheral smear	Bone marrow	Hemostatic Parameters				LFT								
				RBC Count Mil/mm^3	Hb Ing %	PCV %	MCV in fl	MCH in pg	MCHC in %	TC mm^3	DC	Platelet			BT in min	CT in min	Pro thrombin time (sec)	APTT (Seconds)	Sr. Protein (gm%)			Sr. Billirubin (mgm%)			AST (IU)	ALT (IU)	SAP (IU)
																			T	A	G	T	C	U			
1	49	M	16147	4.0	9.4	32	78.0	23.0	29.3	5300	$P_{40}L_{46}E_{14}$	Normal	microcytic Hypochromic	Normal	5'30	8	14	23	5.2	2.1	3.1	3.4	2	1.4	40	32	78
2	29	F	16240	3.5	10.0	33.0	110	33.0	303.0	9300	$P_{72}L_{25}E_{0}$	Low Normal	Normocytic Hypochromic	Normal study	4	6	11	23	5.2	2.1	3.1	3.6	2.2	1.4	46	38	79
3	47	M	16335	2.9	9.1	30	103.4	31.3	30.3	12100	$P_{72}L_{28}E_{0}$	Normal	macrocytosis Target cells	Macronormo blast	4'30	6	15	21	5.2	2.5	2.7	2.4	1.8	0.6	61	47	74
4	4	M	17175	2.5	5.6	21.0	75	25.0	34.0	14800	$P_{50}L_{46}E_{4}$	Mod	Microcytic Hypochromic	Not done	12'15	9	20	35	4.1	2.1	3	2.4	1.8	0.6	63	47	48
5	51	M	17249	2.7	10.0	32	119.0	38.0	32.0	4600	$P_{52}L_{36}E_{2}$	Normal	macrocytosis Target cells	Not done	6' 15	8	15	22	5.8	3	2.8	3.6	2	1.6	53	27	76
6	39	M	17487	3.3	7.8	43.0	87.6	25.1	28.0	2900	$P_{50}L_{46}E_{4}$	Mod	Normocytic Hypochromic	Not done	8'3	8	17	26	3.8	1.8	2	2.2	1.5	0.7	74	59	75
7	48	M	19248	4.2	10.0	33	78.0	25.2	32.1	9200	$P_{62}L_{36}E_{1}M_{1}$	Normal	Hypochromic microcytic	Erythroid Hyperplasia	4'0	5	16	22	5.4	2.5	2.9	3.2	2	1.2	30	22	62
8	34	M	20140	3.8	12.2	32.0	82	23.1	29.0	13500	$P_{65}L_{32}E_{2}$	Normal	Normacytic Hypochromic	Normal study	5	4	13	27	4	1.9	2.1	3.2	2	1.2	69	87	63
9	55	M	21530	4.9	10.0	35	72.0	21.0	29.0	6650	$P_{54}L_{43}E_{3}$	Normal	Hypochromic microcytic	Not done	6'45	9	16	21	5.9	3	2.9	3.2	2.6	0.6	69	97	80
10	36	F	23537	3.4	7.8	32.0	100	25.1	28.0	17000	$P_{78}L_{21}E_{1}$	Normal	Dimorphic anemia	Micro nomoblast	5'30	6	12	25	4	2	2	2.4	1.2	1.2	62	47	66
11	27	M	24148	3.8	11.8	38	100.0	31.0	31.5	9300	$P_{58}L_{40}E_{2}$	Normal	macrocytosis	Macronormo blast	3'30	4	17	23	5.3	2.5	2.7	2.4	1.2	1.2	22	24	88
12	45	M	26670	3.4	7.9	43.0	87.6	25.0	27.2	12200	$P_{72}L_{28}E_{2}$	Low Normal	Normocytic Hypochromic	Not done	8'15	6	16	24	4	1.8	2.2	4.6	3	1.6	92	69	67
13	38	M	27418	2.8	7.2	21	75.0	25.7	34.2	9300	$P_{72}L_{26}E_{2}$	Normal	Normocytic Hypochromic	Not done	12	9	16	24	5	2.1	2.9	4.6	3	1.6	97	102	98
14	38	M	29811	3.8	10.0	34.0	92	2.3.5	25.2	9600	$P_{58}L_{39}E_{3}$	Normal	Normocytic Hypochromic	Not done	8	6'45	14	26	4.9	2.4	2.5	1.1	0.4	0.7	90	66	41
15	48	M	30611	4.9	12.2	43	87.7	25.0	28.3	12300	$P_{72}L_{28}E_{0}$	moderate	Normocytic Hypochromic	Normal	5	6	14	25	5.8	3	2.8	2.9	2.1	0.8	63	37	75
16	33	M	31145	3.9	11.4	35.0	894	30.5	34.0	9200	$P_{54}L_{44}E_{2}$	Mod	Normocytic Hypochromic	Normal	4'15	4	13	26	4.2	2	2.2	2.6	1.9	0.7	63	43	73
17	37	M	33371	3.8	11.0	34	89.4	28.9	32.3	6050	$P_{48}L_{36}E_{10}M_{4}$	Normal	Normocytic Hypochromic	Normal	5'45	5'30	13	21	6	3	3	1.2.	0.8	0.4	56	52	69

18	38	F	34142	+	+	-	+	-	-	+	-	+		-	-	+	mild	mild	-
19	39	M	35179	+	+	-	+	-	+	+	-	-	-	-	-	+	mild	moderate	+
20	48	M	36688	+	+	-	+	+	-	+	+	-	Purpura	+	+	-	Mild	mild	-
21	46	M	37143	+	+	-	+	-	+	-	-	-	-	-	-	-	mild	moderate	+
22	46	F	38190	+	+	+	+	+	+	+	+	-		-	-	-	mild	mild	+
23	35	F	38298	+	+	-	+	+	-	-	+	+	-	-	+	+	mild	moderate	-
24	42	M	39111	+	+	-	+	+	-	+	+	+	Purpura	-	-	+	Mild	moderate	-
25	23	M	39148	+	+	+	+	-	+	-	-	+	-	-	-	+	Gross	Normal	+
26	36	M	40019	+	+	+	+	+	+	-	+	+		-	-	-	Gross	mild	+
27	51	F	40178	+	+	-	+	-	-	-	-	+	-	-	-	+	mild	moderate	-
28	39	F	41211	+	+	-	+	+	+	+	+	+		-	-	+	mild	moderate	-
29	45	F	41379	+	+	-	+	+	+	+	+	+	-	-	-	+	moderate	moderate	+
30	41	M	43311	+	+	-	+	+	-	+	+	+		-	-	+	moderate	moderate	-
31	37	F	43399	+	+	-	+	+	-	-	+	+	-	-	-	+	mild	Normal	-
32	42	M	43571	+	+	-	+	+	-	+	+	+		-	-	-	Mild	mild	-
33	45	M	43611	+	+	+	-	+	-	-	+	-	-	-	-	+	mild	mild	-
34	40	M	43712	+	+	-	+	-	-	+	-			-	-	-	Mild	mild	-

18	38	F	34142	3.3	7.9	38.0	87.2	25.0	28.9	6800	$P_{55}L_{43}E_2$	Mod	Normocytic Hypochromic	Not done	9'30	7'30	16	27	4.9	2.4	2.5	1.1	0.3	0.8	56	52	42
19	39	M	35179	4.1	8.8	31	75.6	21.4	28.3	8600	$P_{60}L_{38}E_2$	Normal	Hypochromic microcytic	Normal	4'30	6	11	23	5.8	3	2.8	1.6	1.2	0.4	38	27	73
20	48	M	36688	2.6	7.2	33.0	78	25.0	32.0	14000	$P_{65}L_{32}E_2$	Mod	Microcytic Hypochromic	Not done	10'30	5	19	33	3.4	1.7	1.7	3.1	2.3	0.8	69	84	76
21	46	M	37143	3.9	9.0	32	82.0	23.0	28.1	8400	$P_{63}L_{37}E_0$	Normal	Normocytic Hypochromic	Not done	6	6'15	16	26	5.3	2.2	3.1	2.4	1.9	0.5	29	27	84
22	46	F	38190	3.3	7.6	41.0	80.1	26.0	32.2	12500	$P_{65}L_{32}E_2$	Mod	Normocytic Hypochromic	Not done	8'30	6'30	14	28	4.9	2.4	2.5	1.8	1	0.8	43	33	81
23	35	M	38298	3.9	11.8	35	89.7	30.2	33.7	3600	$P_{49}L_{46}E_4$	Normal	Normocytic Normochromic	Normal	4'30	6'45	17	21	4.9	3	2.9	3.1	2.7	0.4	87	73	102
24	42	M	39111	3.2	7.4	32.0	76	22.2	29.0	12100	$P_{46}L_{46}M_4E_2$	Normal	Microcytic Hypochromic	Not done	9'0	5'3	17	27	3.6	2	2.6	5.2	3.2	2	98	95	84
25	23	M	39148	3.7	9.8	34	109.6	31.6	28.8	3600	$P_{50}L_{46}E_4$	Normal	Macrocytosis	Not done	5'45	5	17	23	5.6	2.7	2.9	1.6	0.8	0.8	96	67	109
26	36	M	40019	3.8	9.4	39.0	86.4	26.4	30.2	2900	$P_{49}L_{45}E_4M_2$	Mod	Normocytic Hypochromic	Not done	4	6'15	13	26	5.8	2.8	3	3.6	2.4	1.2	87	73	76
27	51	F	40178	3.0	10.0	33	110.0	33.3	30.3	10200	$P_{65}L_{32}E_2$	Normal	Macrocytosis	Normal	6	6'15	14	24	6	3	3	1.4	1	0.4	68	46	79
28	39	F	41211	3.4	7.5	38.0	86	27.6	31.2	9300	$P_{72}L_{26}E_2$	Low Normal	Microcytic Hypochromic	Not done	8'30	5'15	12	25	4	1.9	2.1	4.9	3	1.9	79	74	74
29	45	F	41379	3.7	8.9	35	94.5	24.0	25.4	3400	$P_{46}L_{46}E_3M_1$	Normal	Normocytic Normochromic	Not done	3'45	9'30	14	21	5.6	2.8	2	4.8	3	1.8	102	89	86
30	41	M	43311	3.5	7.4	30.0	77	25.2	32.7	5700	$P_{46}L_{46}E_5M_1$	Mod	Microcytic Hypochromic	Not done	8	5'30	18	24	4.2	2	2.2	3.4	2.6	0.8	66	59	85
31	37	F	43399	3.2	9.8	33	103.0	30.6	29.6	5600	$P_{46}L_{46}E_3M_1$	Normal	Macrocytosis	Macronormo blast	3'30	7	14	26	5.7	2.8	2.9	1.2	0.8	0.4	37	46	66
32	42	M	43571	3.4	7.9	35.0	89	30.5	32.0	2700	$P_{49}L_{45}E_4M_2$	Low Normal	Normocytic Hypochromic	Not done	8'3	5	17	23	4.8	2.3	2.5	2.4	1.4	1	37	46	68
33	45	M	43611	3.7	10.1	31	114.8	37.7	33.0	9200	$P_{62}L_{34}E_4$	Low Normal	Macrocytosis	Macronormo blast	5	6	13	25	5.8	2.9	2.9	1.9	1	0.9	60	40	78
34	40	M	43712	2.6	7.5	38.0	88.1	27.4	31.0	9400	$P_{58}L_{40}E_2$	Low Normal	Microcytic Hypochromic	Not done	8'3	5'30	11	24	4.9	2.4	2.5	1.2	0.5	0.7	38	41	48

35	45	M	43916	+	+	-	+	-	-	-	-	+	-	-	-	-	moderate	Normal	-
36	47	F	44432	+	+	-	+	+	+	+	+	+		-	-	+	moderate	moderate	+
37	36	M	44511	+	+	+	-	-	+	+	-	-	+	-	-	-	mild	Mild	+
38	49	M	44578	+	+	-	+	+	-	-	+	+		-	-	-	Mild	mild	-
39	55	M	44671	+	+	-	+	+	-	-	+	+	+	-	-	+	Gross	moderate	-
40	39	M	44714	+	+	+	+	+	+	+	+	+	Purpura	-	+	-	moderate	Massive	+
41	47	M	45003	+	+	-	+	-	-	-	-	-	-	-	-	+	mild	mild	-
42	42	M	45071	+	+	-	+	-	-	-	-	-	-	-	-	-	mild	moderate	-
43	33	F	45163	+	+	-	+	-	-	-	-	+	-	-	-	-	mild	moderate	-
44	59	M	46611	+	+	-	+	-	-	-	-	-	-	-	-	+	mild	mild	-
45	55	M	47172	+	+	-	+	-	-	-	-	-	-	-	-	-	mild	Normal	-
46	53	M	48164	+	+	-	+	-	-	-	-	-	-	-	-	-	mild	mild	-
47	42	M	50143	+	+	+	+	+	+	-	+	-	-	-	-	+	mild	mild	+
48	35	M	50253	+	+	-	+	+	-	-	+	-	-	-	-	-	mild	moderate	-
49	56	M	50412	+	+	-	+	-	-	-	-	-	-	-	-	+	mild	mild	-
50	35	M	50617	+	+	+	+	+	+	-	+	+	spider	-	-	-	gross	moderate	+

35	45	M	43916	3.5	9.9	34	89.0	31.6	29.1	9800	$P_{70}L_{28}E_2$	Low Normal	microcytic Hypochromic	Macronormo blasts	4'30	5	14	30	5.5	2.7	2.8	2	1.2	0.8	36	38	88
36	47	F	44432	3.2	7.9	35.0	94	24.0	25.2	9300	$P_{62}L_{36}E_1M_1$	Low Normal	Normocytic Hypochromic	Not done	8'15	6	13	23	4.2	1.6	2.6	3.2	2	1.2	61	47	94
37	36	M	44511	2.6	7.5	20	106.0	28.8	37.5	6900	$P_{65}L_{33}E_1M_1$	Normal	Macrocytosis	Macronormo blasts	7	7'30	15	28	4.5	2	2.5	5.2	3.2	2	78	89	92
38	49	M	44578	3.7	9.9	35.0	89	30.2	33.0	5900	$P_{40}L_{46}E_{14}$	Normal	Normocytic Hypochromic	Not done	5	6'30	14	25	4.9	2	2.9	1.8	1	0.8	48	46	50
39	55	M	44671	4.9	13.6	35	89.7	30.8	36.2	9300	$P_{70}L_{30}E_{30}$	Low Normal	Normocytic Normochromic	Normal	6'30	8	12	23	6.1	3	3.1	2.1	1.7	0.4	20	34	91
40	39	M	44714	2.5	5.8	35.0	72	21.0	29.2	15200	$P_{78}L_{21}E_1$	Mod	Microcytic Hypochromic	Not done	11	9	24	36	3.7	1.7	2	4.8	2.8	2	92	70	92
41	47	M	45003	4.3	11.9	38	88.3	27.6	31.3	6600	$P_{67}L_{30}E_3$	Low Normal	microcytic Hypochromic	Micro normo blast	5'15	7'30	11	21	5.9	2	2.9	2.1	1	1.1	36	33	76
42	42	M	45071	4.1	10.0	31	75.6	24.3	32.2	7200	$P_{52}L_{38}E_0$	Normal	microcytic Hypochromic	Erythroid Hyperplasia	4	7	15	28	6.1	3	3	1.6	1	0.6	61	46	86
43	33	F	45163	4.5	12.2	37	90.2	29.7	33.0	9000	$P_{58}L_{39}E_3$	Low Normal	Normocytic Hypochromic	Normal	4'30	6	12	22	6.3	3.1	3.2	2.8	1.7	1.1	52	34	98
44	59	M	46611	2.8	10.0	32	114.2	37.8	33.1	9300	$P_{55}L_{43}E_2$	Normal	Normocytic Hypochromic	Normal	4	6	11	23	5.3	2.4	2.5	5.1	3.1	2	78	67	94
45	55	M	47172	4.5	12.0	39	86.6	26.6	30.7	8600	$P_{62}L_{36}E_2$	Normal	Normocytic Hypochromic	Normal	4	6'15	11	24	6.1	3	3.1	2.6	2	0.6	77	71	48
46	53	M	48164	3.9	9.5	33	84.6	24.3	28.7	7200	$P_{54}L_{44}E_2$	Normal	Normocytic Hypochromic	Normal	6'30	5	11	21	5.1	2	3.1	2.8	1.9	0.9	38	32	46
47	42	M	50143	5.1	13.2	41	80.3	25.8	32.1	12800	$P_{78}L_{21}E_1$	Low Normal	Normocytic Hypochromic	Normal	6'30	6'30	12	24	5.9	2.9	3	3.2	2.2	1	29	33	59
48	35	M	50253	3.9	9.8	30	76.6	25.1	32.6	6900	$P_{58}L_{40}E_2$	Normal	Microcytic Hypochromic	Erythroid Hyperplasia	4	5'30	11	27	6.1	3	3.1	3	3	0.4	29	38	46
49	56	M	50412	4.3	9.5	32	74.4	22.3	30.0	9300	$P_{46}L_{46}E_4E_2$	Low Normal	Microcytic Hypochromic	Erythroid Hyperplasia	6'30	6	13	28	5.7	2.7	3	1.9	1.2	0.7	43	33	67
50	35	M	50617	3.8	10	32	100	33	33.7	6700	$P_{55}L_{39}E_3$	Low normal	macrocytosis target cells	Not done	4	6	11	23	4.6	1.8	1.9	4.9	2.9	2	92	69	66